Papers

Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence

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Abstract

Objectives: To estimate the risk of ischaemic heart disease caused by exposure to environmental tobacco smoke and to explain why the associated excess risk is almost half that of smoking 20 cigarettes per day when the exposure is only about 1% that of smoking.

Design: Meta-analysis of all 19 acceptable published studies of risk of ischaemic heart disease in lifelong non-smokers who live with a smoker and in those who live with a non-smoker, five large prospective studies of smoking and ischaemic heart disease, and studies of platelet aggregation and studies of diet according to exposure to tobacco smoke.

Results: The relative risk of ischaemic heart disease associated with exposure to environmental tobacco smoke was 1.30 (95% confidence interval 1.22 to 1.38) at age 65. At the same age the estimated relative risk associated with smoking one cigarette per day was similar (1.39 (1.18 to 1.64)), while for 20 per day it was 1.78 (1.31 to 2.44). Two separate analyses indicated that non-smokers who live with smokers eat a diet that places them at a 6% higher risk of ischaemic heart disease, so the direct effect of environmental tobacco smoke is to increase risk by 23% (14% to 33%), since 1.30/1.06 = 1.23. Platelet aggregation provides a plausible and quantitatively consistent mechanism for the low dose effect. The increase in platelet aggregation produced experimentally by exposure to environmental tobacco smoke would be expected to have acute effects increasing the risk of ischaemic heart disease by 34%.

Conclusion: Breathing other people's smoke is an important and avoidable cause of ischaemic heart disease, increasing a person's risk by a quarter.

Introduction

Epidemiological studies have shown that the risk of ischaemic heart disease is about 30% greater in non-smokers who live with smokers than in those who do not.[1-5] It seems implausible that the effect of environmental exposure to tobacco smoke should be so large when the excess risk associated with smoking 20 cigarettes per day is only about 80% at age 65 (the average age of ischaemic heart disease events in the studies).[6-12] Environmental exposure to tobacco smoke is only about 1% that of smoking[13-17]; the risk is nearly half. In this paper we examine the possible explanations for this surprisingly large association.

Methods

We carried out five sets of analyses using published data. Firstly, we conducted a meta-analysis of the studies of exposure to environmental tobacco smoke (or passive smoking) and ischaemic heart disease.[18-35] We identified relevant studies through Medline (MeSH terms: smoking, tobacco smoke pollution), by scanning the reference lists of each study and of review articles, and by discussion with colleagues. All the studies used spouse's smoking as an objective measure of exposure to environmental tobacco smoke (non-smokers who live with smokers have greater exposure both inside and outside the home[35 37]). We extracted data on non-fatal infarction or death from ischaemic heart disease in never smokers according to whether their spouses currently smoked or had never smoked, excluding data on ex-smoker spouses where possible. We calculated the average of the relative risk estimates, adjusted for age and sex, of the studies, each weighted by the inverse of its variance (as there was no heterogeneity). For reasons given below in the discussion, we excluded two studies reported together.[35 36]

Secondly, to determine the risk of ischaemic heart disease associated with smoking at low doses, we analysed the dose-response relation between smoking and ischaemic heart disease from five cohort studies of men recruited during the 1950s (selected because of their large size).[6-12] We analysed the five studies separately. In each the smokers had been divided into three or four categories according to the number of cigarettes smoked. We fitted logistic regression lines, in 10 year age groups, of the risk of ischaemic heart disease (relative to non-smokers) on the adjusted average number of cigarettes smoked per day in each smoking category. The number of cigarettes was adjusted as described previously,[38] using data on biochemical markers of tobacco smoke intake to allow for the fact that heavier smokers inhale less from each cigarette on average. From each regression line we determined the risk of ischaemic heart disease associated with smoking one cigarette per day by linear extrapolation. We then calculated the average of the five estimates, weighted (since there was no heterogeneity) by the inverse of variance.

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Thirdly, we used the same cohort studies to determine how much of the excess risk of ischaemic heart disease is reversible many years after stopping smoking, as an indirect estimate of the extent of confounding.

Fourthly, because people exposed to environmental tobacco smoke eat less fruit and vegetables and this is associated with an increased risk of ischaemic heart disease, so confounding will arise,[38 46] we analysed published data to estimate the extent of confounding. We used published estimates of the increase in risk of ischaemic heart disease associated with a decrease of one standard deviation (SD) in consumption of fruit, vegetables, and antioxidant vitamins as markers of fruit and vegetable consumption.[47] We identified studies that measured dietary intake of these nutrients (using weighed dietary inventory or 24 hour recall or food frequency questionnaires with quantitative estimates of portion size)[48-59] in smokers and non-smokers and in non-smokers who lived with smokers and did not (additional MeSH terms: fruit, vegetables, carotene, nutrition surveys, diet surveys, diet records, food habits). We calculated the differences as a proportion of the SD in each study. Thus we estimated the excess risk of ischaemic heart disease attributable to differences in consumption of the nutrients in each study. We also examined the relation between smoking and other risk factors for ischaemic heart disease.

Finally, because of the proposal that platelet aggregation may account for the large effect of exposure to environmental tobacco smoke on risk of ischaemic heart disease,[1] we analysed published data (additional MeSH term: platelet aggregation). We fitted a logistic regression line to the data on risk of ischaemic heart disease according to platelet aggregation[60] and estimated the increase in risk of ischaemic heart disease for a 1 SD increase in platelet aggregation. We determined the effects of smoking and of exposure to environmental tobacco smoke on platelet aggregation (expressed in SDs) from published experimental studies[61-66] and calculated the average increase, weighting by the number of subjects in each study. From these data we estimated the immediate increase in risk of ischaemic heart disease attributable to smoking and exposure to environmental tobacco smoke. We did not use cross sectional studies of platelet aggregation in smokers and non-smokers because they are insensitive[66]; the effects of smoking are short term[67] and may not be apparent in smokers who had not smoked for a few hours before blood was collected.

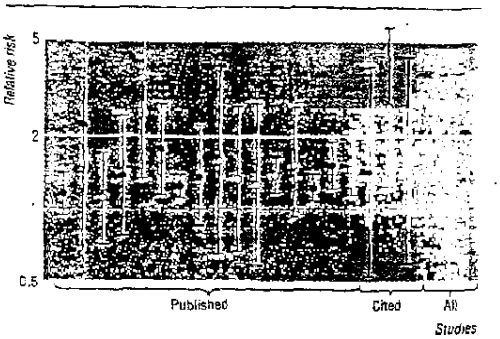

Fig 1 Relative risk estimates (with 95% confidence intervals), adjusted for age and sex, from nine prospective studies (solid circles) and 10 case-control studies (open circles) comparing ischaemic heart disease in lifelong non-smokers whose spouse currently smoked with those whose spouse had never smoked (16 published studies (from left to right[18-33]) and three with results cited by others from abstracts or theses[2 34])

Results

Risk of ischaemic heart disease at low exposure to tobacco smoke

Risk in non-smokers who live with smokers

Figure 1 shows the results of the 19 studies as the risk of ischaemic heart disease in never smokers whose spouses currently smoked relative to the risk in those whose spouses had never smoked (detail of design of the studies has been summarised previously[1 3]).[18-34] There were 6600 ischaemic heart disease events in total. There was no significant heterogeneity ($\chi^2_{25} = 26$), and figure 1 shows that the estimates from the individual studies are consistent with each other. The summary estimate of relative risk was 1.30 (95% confidence interval 1.22 to1.38; $P < 0.001$), similar to the estimates from earlier meta-analyses with fewer studies.[1-5] Summary estimates were similar in women and men in cohort studies (in which almost all ischaemic heart disease events were deaths) and case-control studies (in which most events were non-fatal infarcts) and with or without inclusion of three unpublished studies.

It has been proposed that publication bias accounts for the association.[36] The number of unpublished stud-

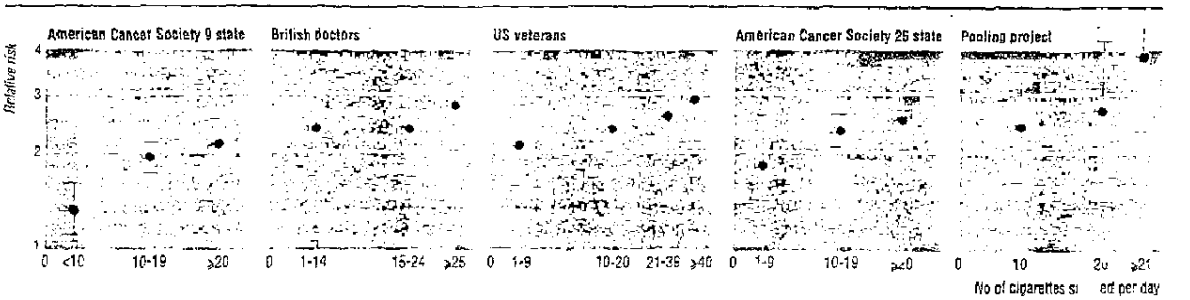

Fig 2 Estimates (with 95% confidence limits) from five studies[6-12] of the risk of ischaemic heart disease in current cigarette smokers according to number of cigarettes smoked relative to never smokers (age standardised to age 65). Scale on the horizontal axis is linear with respect not to the number of cigarettes smoked but to the corresponding concentrations of biochemical markers[33]

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ies would need to be implausibly large. As a simple approximation, eight of the 19 individual studies (fig 1) were significantly positive (a probability for each of less than 1 in 40 if there were no association). The total number of studies needed to generate these by chance would be more than 320 (8 × 40), of which only 19 were published. Exclusion from the analysis of all studies recording fewer than 100 events (as selective publication is more likely to affect small studies) made no difference to the relative risk estimate.

Risk of smoking one cigarette per day

Figure 2 shows the dose-response relation in each of the five studies of smoking and ischaemic heart disease (age standardised to age 65). The risk of ischaemic heart disease increases continuously with daily cigarette consumption, but in all five studies linear extrapolation of the regression line back to zero dose (no cigarettes per day) does not yield the expected relative risk estimate of 1.0. The estimates from the five individual studies of the risk at low dose are consistent with each other, and the weighted average relative risk at one cigarette per day (defining risk in non-smokers as 1.0) was 1.39 (1.18 to 1.64; $P < 0.001$). At 20 cigarettes per day this risk was 1.78.

Table 1 shows the relative risk of ischaemic heart disease associated with smoking one cigarette per day according to age, from the five cohort studies. The estimates decline with increasing age at death ($P < 0.001$). The average age of ischaemic heart disease events in the studies of exposure to environmental tobacco smoke was about 65 years and the estimate of 1.39 is close to the estimate of 1.30 from these studies. With a linear dose-response relation the expected excess risk from smoking one cigarette per day is 4% (1/20th the excess risk of 78% from smoking 20 cigarettes per day); with environmental exposure it is 0.8% (1% of 78%). A high risk at low dose is therefore seen in the studies of smoking (39% excess risk *v* 4% expected) and in studies of environmental exposure (30% *v* 0.8%).

Table 1 Estimated risk (95% confidence interval) of ischaemic heart disease relative to that in unexposed never smokers, from environmental exposure to tobacco smoke (see fig 1) and from actively smoking one cigarette per day (see fig 2)

Age at death (years)	Environmental exposure	Active smoking	
		1 cigarette per day	20 cigarettes per day
45	—	1.93 (0.99 to 3.78)	4.46 (1.21 to 16.42)
55	—	1.64 (0.95 to 2.81)	3.07 (1.06 to 8.88)
65	1.30 (1.22 to 1.38)	1.39 (1.18 to 1.64)	1.78 (1.31 to 2.44)
75	—	1.15 (0.83 to 1.60)	1.34 (0.72 to 2.51)

How much of the association is due to confounding by diet?

Direct estimate

The diet of smokers and of non-smokers who live with them differs from that of non-smokers who live with non-smokers. This dietary difference, rather than the exposure itself, may account for the high risk of ischaemic heart disease.[39 40] The most pronounced difference is a lower consumption of fruit and vegetables,[45 49 51 53 56 57] which contain nutrients that may protect against ischaemic heart disease, including folic acid,[70] potassium, and linoleic acid.[41] These were not measured as potential confounding factors in studies of passive smoking and ischaemic heart disease. Fruit, vegetables, carotenes, vitamin C, and vitamin E are highly correlated with each other, and the regression analyses for each nutrient were not adjusted for these correlations, so each nutrient will serve as a marker for the risk of ischaemic heart disease associated with fruit and vegetable consumption in general, even though β carotene and vitamin E do not themselves reduce mortality from ischaemic heart disease.[41 71 72] Table 2 shows summary estimates from cohort studies of the relative risk of ischaemic heart disease associated with a difference of 1 SD in consumption of all fruit, all vegetables, carotenes, vitamin C, and vitamin E as markers of fruit and vegetable consumption.

Almost all studies showed a lower consumption of these nutrients in active smokers than non-smokers, but the differences were heterogeneous across studies (which is not surprising since fruit and vegetable consumption varies in different communities and different seasons, so the difference between smokers and non-smokers is likely to vary). Table 2 shows, from all studies reporting on each nutrient, the median difference and the largest difference. The estimates of the excess risk of ischaemic heart disease corresponding to the median estimates of the dietary difference in no case exceed 3% (suggesting that diet explains only a 3% excess risk of ischaemic heart disease in smokers); the largest estimates (based on the largest estimate of the dietary difference from any study and the upper confidence limits of the estimates of the association between the nutrients and ischaemic heart disease) do not exceed 9%.

The difference between smokers and non-smokers in plasma low density lipoprotein cholesterol is small—an estimated 0.07 mmol/l,[73] corresponding to an excess risk of ischaemic heart disease (at age 65) of about 3%.[74] The overall excess risk of ischaemic heart disease attributable to dietary differences in smokers (fruit and vegetables and serum cholesterol) is thus about 6%. Blood pressure is no greater in smokers than

Table 2 Estimates of increased risk of ischaemic heart disease in smokers relative to non-smokers, attributable to lower consumption of fruit and vegetables

Marker of consumption of fruit and vegetables	Relative risk of ischaemic heart disease for decrease in consumption of 1 SD[41]	Difference in consumption (smokers minus non-smokers)			Estimate of relative risk of ischaemic heart disease	
			Difference (proportion of 1 SD)			
		No of studies	Median*	Largest	Median	Largest†
All fruit	1.16 (1.02 to 1.31)	5[43 49 51 56 57]	−0.22	−0.33	1.03	1.09
All vegetables	1.23 (1.08 to 1.40)	6[45 49 51 53 56 57]	−0.12	−0.25	1.03	1.09
Carotenes	1.06 (1.03 to 1.11)	5[42-52]	−0.20	−0.34	1.01	1.04
Vitamin C	1.05 (1.00 to 1.09)	13[43-53]	−0.24	−0.49	1.01	1.04
Vitamin E	1.05 (1.02 to 1.10)	6[42-46 53]	−0.12	−0.27	1.01	1.03

*Median differences correspond to consumption lower by 10-15% in smokers than non-smokers.
†Based on upper confidence limit of relative risk estimate and largest difference between smokers and non-smokers.

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Table 3 Risk of death from ischaemic heart disease in men who had stopped smoking for 20 or more years, relative to that in men who had never smoked

Study	No of deaths from ischaemic heart disease: Observed	Expected*	Observed/expected (95% CI)
US Veterans[77]	2478	2303	1.05 (1.01 to 1.09)
American Cancer Society, 25 states[6]	150	141	1.06 (0.90 to 1.25)
British doctors[78]†	200	174	1.15 (1.00 to 1.32)
All studies	2768	2618	1.05 (1.02 to 1.10)

*From rates in never smokers, age adjusted.
†15 or more years.

non-smokers (and body mass index is less); these and other risk factors for ischaemic heart disease have a negligible effect on the relation between smoking and ischaemic heart disease.[75]

For exposure to environmental tobacco smoke the median difference in fruit and vegetable consumption between non-smokers who do and do not live with smokers, based on all available studies (2-3 for each marker), was 0.10 SD for fruit[55 57] 0.06 for vegetables,[53 57] 0.26 for carotenes,[55 58 59] and 0.18 for vitamin C.[53 55 58] These are generally smaller than the median estimates for smokers (table 2). The corresponding estimates of the excess risk of ischaemic heart disease are 1-2%.

The differences in serum cholesterol,[19 21 22 25] blood pressure,[19 21 25] and body mass index[19 21 25 58 59] in never smokers according to whether or not the spouse smoked were imperceptible (as expected since the differences between active smokers and non-smokers are so small). Combining the differences showed no significant difference, with upper confidence limits inconsistent with a serum cholesterol more than 2% higher, blood pressure more than 4% higher, and body mass index more than 6% higher. Estimates of the relative risk of ischaemic heart disease unadjusted and adjusted for blood pressure, serum cholesterol, body mass index, and a measure of social class (published in six epidemiological studies[21-23 25 27 32]) were similar: the weighted average of the adjusted estimates, 1.57 (1.00 to 2.13), was no lower than that of the unadjusted estimates, 1.47 (1.00 to 2.19).

Indirect estimate

Three of the five smoking cohort studies cited above followed the men for 20 or more years. Almost all the excess risk reversed (table 3); the residual excess risk was 6% (2% to 10%). This sets an upper limit to any effect of confounding that is similar to our direct estimate of confounding.

Table 4 Estimates of the extent of confounding and of the cause and effect relation in the associations of passive and active smoking with ischaemic heart disease at age 65

Nature of association	Relative risk of ischaemic heart disease (95% CI): Passive smoking	Active smoking: 1 cigarette per day	20 cigarettes per day
Overall (from figs 1 and 2)*	1.30 (1.22 to 1.38)	1.39 (1.18 to 1.64)	1.78 (1.31 to 2.44)
Irreversible confounding*	1.06 (1.02 to 1.10)	1.06 (1.02 to 1.10)	1.06 (1.02 to 1.10)
Reversible cause and effect	1.23† (1.14 to 1.33)	1.31† (1.11 to 1.55)	1.68† (1.23 to 2.33)

*Estimates of the overall association in passive and active smokers, and of the extent of confounding, all apply to an average age at death of 65 years.
†1.30/1.06=1.23; 1.39/1.05=1.31; 1.78/1.05=1.68. Confidence intervals take those of the "overall" and "confounding" relative risk estimates into account; variances (in logarithms) were added.

People who gave up smoking in recent years also changed their diet.[43 44] We based our analysis on older studies, in which the former smokers would have given up before 1955, when dietary change was not widely advocated on health grounds (indeed, consumption of saturated fat increased in the United States between 1945 and 1955[76]). Significant dietary change in these studies is unlikely but even the recent data on dietary change after stopping smoking[43 44] would increase the estimate of 6% to no more than 12%, similar to the direct estimate of the largest effect.

Size of the causal association

Confounding due to dietary differences accounts for a relative risk estimated as 1.06 in smokers. Of the overall relative risk of ischaemic heart disease associated with environmental exposure to tobacco smoke of 1.30, the estimated relative risk for the causal relation is therefore 1.23 (1.30/1.06). It will in fact be a little higher since dietary confounding is less than in smokers. Even when based on the largest estimate of confounding in smokers it is 1.16 (1.30/1.12). For smoking one cigarette per day the overall relative risk is 1.39 and the estimate of the causal relation is 1.31 (1.39/1.06). Table 4 summarises the estimates.

Mechanism of effect: platelet aggregation

Figure 3 shows the risk of ischaemic heart disease in a cohort of 2398 men (162 of whom had had a myocardial infarction) divided into five groups according to ranked measures of platelet aggregation (from the Caerphilly collaborative heart disease study[60]). The association is linear. The estimate from the logistic regression line fitted to the data was that an increase in platelet aggregation of 1 SD (from any point on the distribution) is associated with a relative risk of ischaemic heart disease of 1.33 (1.19 to 1.48; $P < 0.001$).

Table 5 summarises the experimental studies on smoking and platelet aggregation (from three different research groups).[61-68] The effects of smoking and environmental exposure are similar. The effect of smoking was similar in non-smokers who smoked on the one occasion (for experimental purposes)[63-64] and in habitual smokers abstinent for 8-10 hours.[64-68] From the relation between platelet aggregation and ischaemic heart disease estimated above, the immediate increase in the risk of ischaemic heart disease attributable to effects on platelet aggregation is estimated to be 43% for smoking and 34% for environmental exposure (table 5). These estimates of the immediate effect are, as expected, a little higher than those of the long term effect of intermittent exposure over the day in table 4.

The actions of smoking on other factors that increase risk of ischaemic heart disease are likely to increase continuously with dose such that the effect of exposure to environmental tobacco smoke is imperceptible. Thus plasma fibrinogen concentration is higher in active smokers but not detectably greater in non-smokers who live with smokers than in those who do not (the 95% confidence limits from combining three studies[26 29 79] were 4% lower and 4% higher). The effects on high density lipoprotein cholesterol[21 25] and carboxyhaemoglobin[15 16] are also imperceptible. The more gradual increase in the excess risk from 39% smoking one cigarette per day to 78% at 20 per day (at

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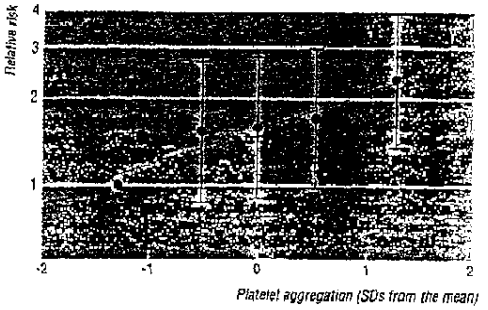

Fig 3 Risk (95% confidence interval) of ischaemic heart disease relative to lowest group according to measurements of platelet aggregation (induced by ADP), expressed as SDs from the mean, with fitted regression line (data from Elwood et al[80])

age 65) is attributable to these and other non-platelet factors.

Discussion

Evidence for a large effect from a small exposure

Environmental exposure to tobacco smoke is associated with an excess risk of ischaemic heart disease of 30% and is estimated to cause an excess risk of 23% (95% confidence interval 14% to 33%), increasing the risk of death from ischaemic heart disease between the ages of 60 and 69 in British men who do not smoke from about 5% to 6%. So large an effect from a relatively small exposure, though unlikely on first impression, is supported by a great deal of evidence.

The association cannot be explained by bias in the studies of environmental exposure to tobacco smoke. Publication bias can be rejected, as discussed above. Misclassification bias arises because some people who claim never to have smoked are former or current smokers; they are at greater risk of ischaemic heart disease and more likely to have spouses who smoke. This bias has been found to be of minor importance in studies of lung cancer[13]; it will be negligible in studies of ischaemic heart disease because the relative risk of ischaemic heart disease in smokers is so much smaller than that of lung cancer (about 2 compared to 20).

The cohort studies of smokers also show a substantial risk at low dose (table 1).

Studies directly measuring the extent of atheromatous disease in arteries have confirmed a similar effect in smokers and in non-smokers exposed to environmental tobacco smoke, and a smaller effect in unexposed non-smokers.[17 80]

The association cannot be explained by confounding. If all the excess risk of ischaemic heart disease in non-smokers who live with smokers compared with those who live with non-smokers were to be explained by their dietary differences, about half the excess risk in smokers would also have to be attributable to differences in diet. The excess risk largely reverses on stopping smoking, indicating that this is not the case. The estimate of the extent of confounding as the excess risk that is not reversed many years after stopping smoking (6%) corroborates the estimate of the excess risk to be expected from the dietary differences.

The effect of tobacco smoke on platelet aggregation provides a plausible mechanism for the low dose effect. The immediate effect of a single environmental exposure is to increase risk by an estimated 34% (table 5). This will be an underestimate because of regression dilution bias (which could not be allowed for because repeat measures were not available), but will also tend to be an overestimate because it does not reflect typical intermittent exposure to environmental tobacco smoke over the day, which will be somewhat less. One hour after a single exposure the effect on platelet aggregation is attenuated by about half,[67] so the likely effect of intermittent exposure throughout the day could be consistent with our estimate of a 23% increase in risk. Simple corroboration is provided by the observation that aspirin abolishes the effect of tobacco smoke on platelet aggregation[65 68] and reduces the risk of ischaemic heart disease by about 25%.[81] The experimental evidence of a similar effect of smoking and environmental exposure on platelet aggregation is corroborated by studies showing that the generation of thromboxane A_2 from arachidonic acid (which leads to platelet aggregation) was also similar.[82] A small dose of an agonist seems to have a maximal effect on platelet aggregation.[83]

A meta-analysis of the studies of occupational exposure to environmental tobacco smoke exposure indicated a disproportionately large effect: relative risk 1.36 (1.08 to 1.71).[84] The occupational studies lack the susceptibility to confounding because non-smokers who work with smokers will not share their diet.

In animal experiments, eight studies on four species (involving exposure to the smoke from simultaneous combustion of between one and 10 cigarettes, generally for 4-6 hours per day over 6-16 weeks) all showed pronounced vascular toxicity of the

Table 5 Results of experiments of exposure to tobacco smoke and platelet aggregation and the associated immediate increase in risk of ischaemic heart disease

Exposure	Change in platelet aggregation ratio after exposure†		Associated relative risk of ischaemic heart disease (95%CI)‡
	Absolute	No of standard deviations	
Unexposed control period (non-smokers, n=10[81])	0	0	1.00
Environmental tobacco smoke(20 minutes, n=10[81])	0.09*	1.03	1.34 (1.19 to 1.50)*
Active smoking: smoking one[68] or two[82-87] cigarettes (average of 6 studies, n=158)	0.11*	1.25	1.43 (1.24 to 1.63)*

*P≤0.001.
†Absolute change is an estimate of the proportion of all circulating platelets that were incorporated into aggregates as a result of the exposure; platelet aggregation ratios were on average 0.83 before and 0.72 after active smoking.
‡From the association between platelet aggregation and ischaemic heart disease shown in figure 3.

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exposure.[85-92] The size of the resulting infarct after experimental occlusion of a coronary artery was 50-100% greater[85-87] and arterial atheromatous disease was about twice as extensive[88-92] in exposed animals than in unexposed controls.

Evidence against a large effect at low dose

Pipe and cigar smokers have a low risk of ischaemic heart disease (the risk relative to non-smokers was estimated as 1.13 for pipe smokers, 1.30 for cigar smokers, and 1.75 for cigarette smokers[93]). Pipe and cigar smokers tend not to inhale when smoking and because of characteristics of the smoke can absorb nicotine through the mouth,[93] but they must inhale their own environmental tobacco smoke in the same way that non-smokers inhale other people's smoke. Their low risk might at first sight weigh against the view that inhaling environmental tobacco smoke poses a material risk of ischaemic heart disease. However, men who smoke only pipes or cigars smoke much less frequently than cigarette smokers. In a study of 21 520 men, 2618 current pipe or cigar smokers smoked on average three times a day whereas 4184 cigarette smokers smoked on average 20 times a day.[94] The difference in this frequency, in view of the short term nature of the effect on platelet aggregation (half life less than an hour[57]), may well reconcile the observations of passive smokers and the risk of ischaemic heart disease among pipe smokers.

Excluded studies

A separate analysis of one of the studies of environmental tobacco smoke exposure and ischaemic heart disease in the set of 19 studies (fig 1), and of two data sets not published elsewhere (from the US National Center for Health Statistics and the American Cancer Society) has been published by Layard and LeVois, consultants to the tobacco industry.[35 36] They reported a combined relative risk estimate from the three studies of 1.00, with a narrow 95% confidence interval (0.97 to 1.04).[36] This negative result is statistically inconsistent with the estimate of 1.30 (1.22 to 1.38) from the above analysis of 19 studies ($P < 0.001$). The difference is too great for the two groups of studies to be combined as separate valid estimates; one must be flawed. We took the estimate from the 19 studies as valid and rejected that of Layard and LeVois, since there is no reason to reject an analysis based on 19 independent studies in favour of one from a single group with a vested interest.

Direct evidence supports this decision. Firstly, in one of the three studies the relative risk estimate (men and women combined) of Layard and LeVois of 0.98 (0.90 to 1.07)[36] was inconsistent with that from an independent analysis of the same data commissioned by the American Cancer Society (the owners of the data) of 1.21 (1.06 to 1.38).[31] Secondly, even in the absence of a causal effect, the combined estimate of 1.00 is inconsistent with any confounding from the dietary differences. Thirdly, the result is inconsistent with the data on low dose active smoking, the evidence on platelet aggregation, the animal studies and the other evidence summarised above.

Key messages

- Analysis of 19 epidemiological studies shows that people who have never smoked have an estimated 30% greater risk of ischaemic heart disease if they live with a smoker ($P < 0.001$)
- This is surprisingly large—almost half the risk of smoking 20 cigarettes per day even though the exposure is only 1% of that of a smoker
- The excess risk from smoking one cigarette per day is 39%—similar to the risk in a non-smoker living with a smoker
- The effect is mainly explained by a non-linear dose-response relation between expsoure to tobacco smoke and risk of heart disease
- Detailed analysis shows no significant bias; dietary confounding can account for an excess risk of only 6%, so revising the excess risk from 30% to 23%

Conclusions

We believe that there is no satisfactory alternative interpretation of the evidence reviewed here than that environmental exposure to tobacco smoke causes an increase in risk of ischaemic heart disease of the order of 25%. In proportionate terms this is of similar magnitude to the effects of exposure to environmental tobacco smoke on lung cancer,[15] but the number of excess deaths from heart disease will be far greater because heart disease is so much more common than lung cancer in non-smokers. Reversal of the effect would reduce the risk of ischaemic heart disease by about as much as taking aspirin, or by what many people could achieve through dietary change. The effect of environmental tobacco smoke is not trivial, as is often thought. It is a serious environmental hazard, and one that is easily avoided. The evidence on ischaemic heart disease warrants further action in preventing smoking in public buildings and enclosed working environments. The hazard in the home requires greater public education so that smokers recognise the risk to which they expose members of their family. It is also important that clinicians advise that families of patients with known coronary artery disease do not smoke in their presence.

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The accumulated evidence on lung cancer and environmental tobacco smoke

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Abstract

Objective: To estimate the risk of lung cancer in lifelong non-smokers exposed to environmental tobacco smoke.

Design: Analysis of 37 published epidemiological studies of the risk of lung cancer (4626 cases) in non-smokers who did and did not live with a smoker. The risk estimate was compared with that from linear extrapolation of the risk in smokers using seven studies of biochemical markers of tobacco smoke intake.

Main outcome measure: Relative risk of lung cancer in lifelong non-smokers according to whether the spouse currently smoked or had never smoked.

Results: The excess risk of lung cancer was 24% (95% confidence interval 13% to 36%) in non-smokers who lived with a smoker ($P < 0.001$). Adjustment for the effects of bias (positive and negative) and dietary confounding had little overall effect: the adjusted excess risk was 26% (7% to 47%). The dose-response relation of the risk of lung cancer with both the number of cigarettes smoked by the spouse and the duration of exposure was significant. The excess risk derived by linear extrapolation from that in smokers was 19%, similar to the direct estimate of 26%.

Conclusion: The epidemiological and biochemical evidence on exposure to environmental tobacco smoke, with the supporting evidence of tobacco specific carcinogens in the blood and urine of non-smokers exposed to environmental tobacco smoke, provides compelling confirmation that breathing other people's tobacco smoke is a cause of lung cancer.

Introduction

Ten years ago scientific committees and national organisations concluded that exposure to environmental tobacco smoke (also called passive smoking) is a cause of lung cancer.[1-4] Substantial additional evidence has since been published, and we report a new analysis. The additional data permit a more precise estimate of the size of the association, with a further assessment of whether it is cause and effect by seeking a dose-response relation and examining whether sources of bias and confounding could account for the association. We also compared the direct estimate of risk from epidemiological studies with that from a low dose linear extrapolation of the risk in smokers using biochemical markers of exposure to tobacco smoke.

As before,[5] the estimate of effect was the relative risk of lung cancer in lifelong non-smokers according to whether the spouse currently smoked or had never smoked. Spousal exposure is the best available measure: it is well defined and has been validated using biochemical markers.[6-9] It reflects exposure in general because non-smokers who live with smokers tend to be more exposed to tobacco smoke from other sources, because they are more likely to mix socially with smokers.[6] Workplace exposure varies considerably and is difficult to measure.

Methods

Direct estimate of risk of lung cancer from epidemiological studies

Studies of environmental tobacco smoke and lung cancer were identified from Medline, the citations in each study, and consultation with colleagues. We

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